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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/379,308	08/23/1999	PHILIPPE DIAZ	016800-318	1123

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EXAMINER	
LUKTON, DAVID	
ART UNIT	PAPER NUMBER
1653	

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23

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/379,308	Diaz
Examiner	**Art Unit**
David Lukton	1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Jul 25, 2002 .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 60-104 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 60-104 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 22
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Pursuant to the directives of paper No. 20 (filed 2/19/02), claims 42, 54, 56-58 were amended. Subsequently, paper No. 21 (filed 7/25/02) directed the cancellation of claims 42-59, and the addition of claims 60-104. Claims 60-104 are pending.

Applicants' arguments filed 2/19/02 and 7/25/02 have been considered and found not persuasive.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 75-79 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 75 recites a method for "inhibiting differentiation of keratinocytes". It is not clear where support for this may be found. The term "differentiation" occurs at four locations. (In USP 5,981,776, those locations are the following: col 1, line 15; col 7, line 66; col 8, line 4; col 8, line 6, and col 8, line 36+). There are two issues here. First, where in the specification would one conclude that the compounds are effective to inhibit differentiation

of a given cell type, rather than promote differentiation? And second, where is it stated that this inhibition of differentation applies specifically to keratinocytes?

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 60-104 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants have submitted an abstract (paper No. 11, filed 9/18/00), Michel Demarchez has presented a few results of *in vitro* studies, and offered general conclusions based thereon.

First, the declaration makes reference to Bailly (*Skin Pharmacol* **3**, 256, 1990). This reference discloses experiments in which various compounds were tested for their propensity to induce secretion of plasminogen activator (PA) in F9 murine embryonal carcinoma cells.

The reference also states that the induction of PA secretion correlates with morphological changes occuring in treated embryonal carcinoma cells, and provides a means to monitor F9 differentiation. The authors of the article applied the label "retinoid" to the tested compounds. Also stated (p. 264) is that (a) it is not known which RA receptors are

involved in the induction of PA in F9 cells, (b) the mechanism of PA induction by retinoids has not been elucidated, and (c) the capacity of each retinoid to induce a biological response... is not related to either the AC_{50} parameter or to receptor affinity. Notably absent is even an assertion that any of the disorders recited in claims 42-55 can be successfully treated by any of their tested compounds. Next, the declaration argues that, using assays described in Levin (*Nature* **355** 359, 1992) and in Allenby (*Proc. Natl. Acad. Sci.* **90**, 30, 1993), two of the compounds of claims 42-55 were tested for RXR binding, "RXR transactivation", and "RXR transactivation AC". It is not clear what is meant by "RXR transactivation", and "RXR transactivation AC"; perhaps applicants prepared a CRBPII-RXRE-CAT reporter plasmid, and perhaps not. It is also not clear exactly what "RXR binding" refers to; Levin makes reference to three subtypes of RAR receptors, i.e., RARα, RARβ, RARγ. Which receptor subtypes are encompassed by the term "RXR binding" ...? Is this RXRα, or a mixture of subtypes? Next, the declaration points to Safonova (*Biochem Biophys Res Commun* **204**, 498, 1994), and argues that this reference discloses the usage of "such agonists" on cell differentiation and potential therapeutic utility. This reference discloses that a compound to which the label "retinoid" has been applied stimulated glycerol-3-phosphate dehydrogenase activity, and that the compound "CD367" stimulated expression of RARα, RARβ, and RARγ. It is not clear that the "such agonists" disclosed in Safonova are the same as the "such agonists" disclosed in Bailly,

Allenby or Levin, but even if they are, Safonova does not assert that any of the compounds which stimulate stimulated glycerol-3-phosphate dehydrogenase activity, or which stimulate expression of RARα, RARβ, and RARγ can be used to treat even one of the disorders recited in instant claims 42-55.

Next, the declaration has pointed to Hong (*Retinoids and Human Cancer*, 1994). No pages numbers are given. However, the copy of pages 598-623 does not show that there is even one compound which exhibits any of the *in vitro* activities described in Bailly, Allenby or Levin, nor is there an assertion that there exists a compound which exhibits any of the *in vitro* activities described in Bailly, Allenby or Levin, and at the same time can be used to treat any of the disorders recited in instant claims 42-55. It may be the case that some therapeutic utility exists for vitamin A itself, but none of the claims is drawn to a therapeutic use of vitamin A.

Next, the declaration has pointed to Lippman and DiGiovanna (Retinoids in Skin Cancer). Again, no page numbers were indicated. However, the copy of pages 179-196 (provided by applicants) was considered. The reference does discuss experiments with 13-cis retinoic acid (isotretinoin); it may well be the case that this particular agent is efficacious in the treatment of one or more dermatological disorders; but again, there is no connection between applicants *in vitro* data, or that of Bailly, Allenby or Levin (on the one hand), and an attribution of the pharmacological effects of 13-cis retinoic acid to applicants' *in vitro*

data (on the other hand).

Next, the declaration has pointed to Kavanagh (*Retinoids and Cervical Cancer*). Again, no page numbers were specified. However, pages 271-280 were considered. It is true that the authors have suggested some efficacy of all-*trans*-retinoic acid in the treatment of cervical dysplasia, and possibly some benefit following administration of 13-cis retinoic acid to patients with invasive cervical cancer. But again, it is not apparent that (a) there is a property shared by both retinoic acid and applicants' compounds that is manifest in an *in vitro* biochemical assay, and (b) that the presence or absence of this property which is so manifest correlates with the efficacy of compounds in therapeutic applications.

Next, the declaration has pointed to Meyskens (*J. Am. Acad. Dermatol.* **15** , 822, 1986). The authors do indicate that some histological changes in patients afflicted with dysplastic nevus syndrome occurred following topical administration of tretinoin. Again, no connection is drawn between applicants' *in vitro* assays, and treatment of dysplastic nevus syndrome.

What applicants have done is first, to undertake experiments which justify applying the label of "retinoid" to their compounds, and second, to point to experiments which have been done on AT retinoic acid, and 13-cis retinoic acid, and have argued that since the label "retinoid" can be applied to AT retinoic acid and 13-cis retinoic acid, that therefore any compound to which the label "retinoid" can be applied is going to be effective in treating

cancer, and all the other disorders recited in the claims. However, this argument is found to be entirely unconvincing. Certainly, the term "retinoid" is commonly used by chemists and biologists. But there is no agreed upon standard as to what the structural, biochemical or physical properties might be that are either necessary or sufficient for a compound to be classified in this way. In addition, where the line might be drawn exactly between a "retinoid" and a "non-retinoid" remains to be determined. Some chemists might apply the term "retinoid" because the UV/VIS spectrophotometric properties of a given compound are similar to retinal. Another chemist might apply the term "retinoid" because a compound shares one or more biochemical traits exhibited by 13-cis retinoic acid in halophilic bacteria (bacteriorhodopsin). Still another might apply the term "retinoid" to a compound such as all-*trans*-retinoyl fluoride because of its ability to inhibit opsin in the visual cycle (see, e.g., Wong, C. G., "Inactivation of bovine opsin by all-*trans*-retinoyl fluoride", *J. Am. Chem. Soc.* **104**, 7374-75, 1982). Another chemist might apply the term "retinoid" to a group of compounds which exhibit similar anti-oxidant activity (similar to retinol) in a given assay. A botanist may have another view entirely of what a "retinoid" is. Accordingly, merely because applicants have made an argument that the term "retinoid" can be applied to their (synthetic) compounds, and because one or two naturally occurring retinoids happen to exhibit some efficacy in the treatment of a given disease or two does not mean that applicants compounds are imbued with the property of being effective in the treatment of

even one of the disorders named in the claims. On the other hand, the possibility still remains that it is well known in the art that if a compound can induce secretion of plasminogen activator in F9 murine embryonal carcinoma cells, and can also "activate" one or more classes of RXR receptors, the compound will be effective in the treatment of one of the recited disorders, and further, that the efficacy *in vitro* correlates with the degree of efficacy *in vivo*.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. Even if it is true that the compounds (to which the claims are drawn) are in fact "retinoids", all retininoids do not exhibit the same activities, either *in vitro* or *in vivo*, and moreover, many retinoids are in fact ineffective in treatment of various proliferative disorders.

Consider the following references, and their teachings:

- Benedetti (*BLOOD* **87** (5) 1939-50, 1996) discloses that "RAR- and RAR *alpha*-selective retinoids were able to induce growth arrest, granulocytic differentiation, and type II TGase, whereas the RXR-selective retinoid SR11217 was inactive". Applicants have asserted that the compounds of examples 2 and 4 function as RXR agonists. This reference supports the proposition that RXR-selective retinoids can be inactive.

- Byers S (*ENDOCRINOLOGY* **137** (8) 3265-73, 1996) discloses that "A retinoid X

receptor-specific ligand was ineffective". This reference supports the proposition that RXR-selective retinoids can be inactive.

- Chandraratna R A (*journal of the American Academy of Dermatology* 37 (2 Pt 3), S12-S17, 1997) discloses that tazarotene selectively transactivates RAR *beta* and RAR *gamma* subtypes and is inactive at retinoid X receptors (RXRs). This reference is cited to merely reinforce the fact that there is a distinction between RAR's and RXR's and that compounds to which the term "retinoid" is applied would have to be divided, at a bear minimum, into at least two separate categories; what may be true of one is not necessarily going to be true of the other.

- Chen S et al., (*Journal of Pharmacy and Pharmacology* **47** (8) 626-31, 1995) discloses that "BMS-181163 (4-acetamidophenyl retinoate, previously reported as BMY-30123), the acetamidophenyl ester of all-trans-retinoic acid (tRA), is ... ineffective for the treatment of acne in patients." Thus, a compound to which the label "retinoid" has been applied is ineffective in the treatment of at least one skin disorder.

- Dockx P. (*British Journal of Dermatology* **133** (3) 426-32, 1995) discloses that "retinoids derived from retinol or beta-carotene are inactivated, among other ways, by enzymes belonging to the P450 cytochrome group". This reference illustrates one of the pitfalls in attempting to extrapolate from *in vitro* experiments to *in vivo* therapies. Applicants' disclosed compounds could very well be inactivated by one or more P-450 isozymes. The term cytochrome P-450 refers not to a single enzyme, but rather a group of hundreds of thousands, if not millions of isozymes. Moreover, the isozymes are induced in response to xenobiotics, and the particular isozymes which may be induced cannot be predicted from the structure of the compound.

- Elder J T et al., (*Journal of Investigative Dermatology* **106** (3) 517-21, 1996) discloses (page 519) that binding affinity for RAR receptors does not correlate with *in vivo* assays or other *in vitro* assays.

- Kinoshita et al. (*Blood*, **95** (9) 2821-8, 2000) discloses results of in vitro assays conducted on a series of retinoids. At least one of the RXR-selective agonists was inactive. This reference is cited to reinforce the examiner's position that "retinoids" do not constitute a monolithic entity; compounds belonging to this group span a diverse spectrum of in vitro activities. Accordingly, attempting to extrapolate from

the activities of one "retinoid" to another constitutes a tenuous proposition.

- Miller W. H. et al., (*Blood* **85** (11) 3021-7, 1995) discloses results of a study of treatment of patients afflicted with leukemia. Miller reports that despite achieving favorable results *in vitro*, only one patient in seven achieved remission. This reference supports the assertion of "unpredictability" in the extrapolation from *in vitro* data to a therapeutic intervention.

- Muccio D. et al. (*J. Med Chem.* **41** (10) 1679-87, 1998) discloses that at least one compound was effective at binding to RAR, but was not effective at activating RAR. This supports the assertion that mere binding to a receptor is not a reliable indicator of activity. In addition, data presented (e.g., table 3) supports the contention that retinoid/receptor interactions are very specific, very exacting, and above all, very unpredictable.

- Paraskevaidis A et al. (*DERMATOLOGY* **196** (1) 171-5. 1998) discloses that "...the biological efficacy of ... retinoids could be greatly impaired by their rapid metabolism to inactive compounds"

- Sakaue et al. (*MOLECULAR PHARMACOLOGY* **55** (4) 668-76, 1999) discloses (e.g., page 673) that AHPN, although a retinoid, does not exhibit growth arrest and apoptosis via the RAR or RXR receptor. This brings up the point that the biological activities of "retinoids" do not necessary correlate with their ability to interact with retinoid receptors. Accordingly, extrapolation from studies on RAR or RXR is "unpredictable". Moreover, the compound AHPN, although a retinoid, behaved differently from retinoic acid in various assays.

- Shiohara M et al. (*Blood* **93** (6) 2057-66, 1999) discloses that SR11363 (Retinoid B) was inactive in a cell assay, even though this compound selectively activated RAR-*beta* and *gamma*.

- Sun S Y et al. (*CANCER RESEARCH* **57** (21) 4931-9, 1997) discloses that several RXR selective retinoids were inactive in a carcinoma cell assay. This supports the assertion that assays based only on interaction with the RXR receptor are unreliable indicators of activity in proliferative disorders.

- Tashima T et al (*CHEMICAL AND PHARMACEUTICAL BULLETIN* **45** (11) 1805-13, 1997) presents data on various retinoids, a few of which were inactive. This

reference supports the proposition that structure/activity relationships *in vitro* are unpredictable.

- Tockman, (*IARC SCIENTIFIC PUBLICATIONS* **154** 257-70, 2001) discloses that in trials with lung cancer end-points, administration of retinoids either was ineffective or, in the case of beta-carotene, led to greater lung cancer incidence and mortality. The reference also supports the proposition that extrapolating from animal models to humans is unpredictable.

- Wan H et al., (*CANCER RESEARCH*, **61** (2) 556-64, 2001) discloses that "nuclear retinoic acid receptors (RARs) and retinoid X receptors (RXRs)... mediate most of the effects of retinoids on cell growth and differentiation. Despite expressing abundant levels of RAR *beta* mRNA, lung adenocarcinoma H1792 cells are resistant to the growth-inhibitory effects of all-trans-retinoic acid...". Thus, studies of interactions between retinoids are not necessarily a reliable indicator of *in vivo* activity.

- Weinstein G. D., et al. (*Journal of the American Academy of Dermatology* **37** (1) 85-92, 1997) discloses that "Previous topical retinoids have generally been either ineffective or too irritating for therapy of psoriasis". Thus, this reference teaches that there exist compounds to which the label "retinoid" has been applied, and yet which are not effective in the treatment of psoriasis.

Thus, the foregoing conclusions may be drawn from the references cited by the examiner: (a) "retinoids" do not constitute a monolithic entity; what may be true for one retinoid in an *in vitro* assay is not necessarily true for another. Similarly, what may be true for one retinoid in an *in vivo* assay is not necessarily true for another. (b) structure/activity relationships *in vitro* are unpredictable; (c) several retinoids are known in the art to be ineffective in the treatment of various proliferative and skin disorders; (d) some compounds which have been termed "retinoids" may exert their effects by mechanisms which are independent of the RAR and RXR receptors; (e) retinoids are often inactivated by

cytochrome P-450 *in vivo*, and the extent of that inactivation is unpredictable.

In applicants' response filed 6/28/01, applicants responded to the examiner's observation that the mechanism of PA induction by retinoids has not been elucidated (Bailly et al.) applicants have conceded that this is true, but that it remains the case that PA induction occurs. The examiner would respond by arguing that (a) there are no *in vitro* assays for retinoids which constitute a reliable predictor of any therapeutic efficacy and (b) applicants *in vitro* data is rather murky as to exactly what was done, how it was done, and what it means. The very foundation upon which applicants are attempting to extrapolate from is very tenuous. It is not disputed that applicants have obtained an "AC 50" value or a value in the "RXR transactivation test", but what do these numbers mean? As for the "PA induction", if the mechanism is unknown, upon what basis are applicants attempting to extrapolate from it?

In response to the foregoing, applicants have amended the claims. However, each of the claims still makes reference to **treatment** of a disorder (e.g., "treat[ment of] said disorder" or "treat[ment of] cancer" or "treat[ment of] said inflammation"). Use of the term "treatment" in this way conveys an assertion of therapeutic efficacy, which is not in evidence. In addition, other claims assert that the following can be "inhibited": inflammation, aging, dermal atrophy, cicatrization, and alopecia. However, the term "inhibiting", when applied to a disease, is regarded as similar in effect to "treating" the disease. From the

standpoint of enablement, there is little difference between an applicant who asserts that he can "inhibit" disease "X", and an applicant who asserts that he can "treat" disease "X". As for inhibiting aging, there is no evidence that applicants have been able to achieve this, and moreover, there is no evidence that anyone else has achieved it either. Accordingly, the enablement rejection is maintained against all claims.

In response to the previously imposed enablement rejection, applicants have offered further comments on the Michel Demarchez declaration (paper No. 11, filed 9/18/00). It is asserted that the compound of example 2 is an RAR-agonist. However, no reason for this assertion is given. Next, it is argued that, in accordance with the procedure disclosed in Bailly (*Skin Pharmacol* **3**, 256, 1990), the compound of example 2 was effective to promote production of plasminogen activator in F9 murine ebryonal carcinoma cells *in vitro*. Next, applicants have argued that the compound of example 2 "transactivates" RARs. No explanation of the term "transactivates" is offered, and none is evident. Next, applicants assert that the "activation" of RAR-*alpha*, *beta* and *gamma* is 96%, 87% and 78%, respectively. However, there is no suggestion as to what exactly "activation" means, or how it was determined. Nevertheless it is stipulated by the examiner that some sort of *in vitro* experiment was done. What the results may have been, how they were obtained, and what conclusions can be drawn with regard to *in vitro* processes cannot be determined at this time. Next, applicants argue that the compound of example 2

"transactivates" RARs. No explanation of the term "transactivates" is offered. Also, no explanation is given as to how the value of Kd <10,000 nM might have been obtained, or what the connection between a value of 10,000 nM (on the one hand) and the phenomenon of transactivation might be. Next, it is argued that the compound of example 6 exhibited an AC_{50} of less than 10,000 nM. How this number might have been obtained is not clear. Perhaps what was undertaken was an assay of the propensity of the compound to promote production of plasminogen activator in F9 murine embryonal carcinoma cells *in vitro*. Or perhaps it was some other assay. Next, applicants make another reference to "transactivation", but without explanation. Next, applicants refer again to the Demarchez declaration (paper No. 11, filed 9/18/00) and have argued that somewhere in the declaration there is an explanation of the "transactivation test". However, while the term "RXR "transactivation test" occurs one time in table 2, there is no specific explanation of what it means, or how any of the numbers were obtained. What declarant has done is to suggest that somewhere within the text of two different documents can be found a procedure which was followed. However, which procedure was followed has never been made clear. Applicants go on to conclude that the "efficacy of retinoid compounds as pharmaceutical agents is accepted in the art".

Applicants attempt to comment on the "AC_{50}" numbers and the "RXR "transactivation test" have only resulted in an increase in the level of confusion, not a decrease. If

applicants believe that their experiments are somehow relevant to therapeutic methods, it is suggested that applicants provide a detailed explanation of how each experiment was conducted. If the argument is made that an experimental procedure can be found in a given journal article, it would help to specify the exact passage(s) in question, since journal articles often recite several different procedures.

It may be the case that one or more of the claimed compounds exhibits some sort of effect on plasminogen activator production in a given cell line, or that one or more of the claimed compounds binds to one receptor or another. However, applicants have made no attempt to correlate either of these with any of the recited therapeutic methods. It may be the case that other scientists, working with compounds which are very different from those claimed, have experienced some success in the treatment of a given disease or disorder, and that they applied the label "retinoid" to their compounds. But the fact that there may be one or two or even ten such compounds has only limited relevance to the fundamental issue, which is that of correlation between the *in vitro* experiments undertaken by applicants (on the one hand) and therapeutic efficacy (on the othe hand). A first step in the process would be for applicants to provide examples of compounds which promote secretion of plasminogen activator in F9 murine embryonal carcinoma cells and which are therapeutically effective (in accordance with the claims). This would only be a first step, but applicants have not taken it. And if this first step were undertaken, there would still remain the fundamental

issue of "unpredictability". This issue is addressed in each of the following references:

Benedetti (*Blood* **87** (5) 1939-50, 1996)

Byers S (*Endocrinology* **137** (8) 3265-73, 1996)

Chandraratna R A (*Journal of the American Academy of Dermatology* 37 (2 Pt 3), S12-S17, 1997)

Chen S et al., (*Journal of Pharmacy and Pharmacology* **47** (8) 626-31, 1995)

Dockx P. (*British Journal of Dermatology* **133** (3) 426-32, 1995)

Elder J T et al., (*Journal of Investigative Dermatology* **106** (3) 517-21, 1996)

Kinoshita et al. (*Blood*, **95** (9) 2821-8, 2000)

Miller W. H. et al., (*Blood* **85** (11) 3021-7, 1995)

Muccio D. et al. (*J. Med Chem.* **41** (10) 1679-87, 1998)

Paraskevaidis A et al. (*DERMATOLOGY* **196** (1) 171-5. 1998)

Sakaue et al. (*MOLECULAR PHARMACOLOGY* **55** (4) 668-76, 1999)

Shiohara M et al. (*Blood* **93** (6) 2057-66, 1999) discloses that SR11363 (Retinoid B)

Sun S Y et al. (*CANCER RESEARCH* **57** (21) 4931-9, 1997)

Tashima T et al (*CHEMICAL AND PHARMACEUTICAL BULLETIN* **45** (11) 1805-13, 1997)

Tockman, (*IARC SCIENTIFIC PUBLICATIONS* **154** 257-70, 2001)

Wan H et al., (*Cancer Research* **61** (2) 556-64, 2001)

Weinstein G. D., et al. (*Journal of the American Academy of Dermatology* **37** (1) 85-92, 1997)

What is suggested is for applicants to take a position on the question of whether *in vitro* data (obtained on retinoids) is predictive of therapeutic efficacy. If applicants believe that *in vitro* data (obtained on retinoids) is indeed predictive of therapeutic efficacy, then it is suggested that applicants read through each of the references cited by the examiner, and explain how it is that they could have predicted the failure of each retinoid to be therapeutically effictive. If these steps are undertaken, it may help to advance the prosecution. However, an alternative to this would be to amend some of the claims and to cancel others, as follows. What is suggested is (a) delete reference to "treat[ment] of said cancer" in claim 60, (b) delete reference to "treat[ment] of said disorder " in each of claims 65-75, and (c) cancel each of claims 80-104.

*

Claims 60-104 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the independent claims, the term "inflicted" is used. It may be that the term *afflicted* is intended instead.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1800